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Dynamic Kinetic Asymmetric Transformations of β-Stereogenic-α-Keto Esters via Direct Aldolization

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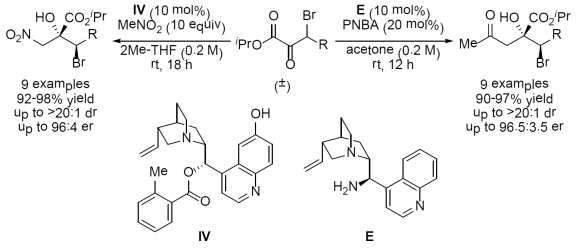
Abstract



Dynamic kinetic asymmetric transformations (DyKAT) of racemic β-bromo-α-keto esters via direct aldolization of nitromethane and acetone provide access to fully substituted α-glycolic acid derivatives bearing a β-stereocenter. The aldol adducts are obtained in excellent yield with high relative and absolute stereocontrol under mild reaction conditions. Mechanistic studies determined that the reactions proceed through a facile catalyst-mediated racemization of the β-bromo-α-keto esters under a DyKAT Type I manifold.

Keywords

dynamic kinetic asymmetric transformation (DyKAT); Henry reaction; acetone aldol; organocatalyzed; α-keto ester

Deracemization is a valuable method for the generation of chiral molecules from simple racemic starting materials.[1] While there are a plethora of reported dynamic kinetic processes, most are arguably either complexity-neutral transformations (hydrogenation, acylation, etc.) or generate a single chiral center. Dynamic kinetic asymmetric transformations (DyKAT) that utilize a C–C bond forming step in the construction of multiple stereocenters are highly valuable synthetic strategies.[2] In this communication, we describe dynamic kinetic asymmetric transformations of racemic β-bromo-α-keto esters via direct aldolization employing both nitromethane and acetone.[3]

Based on Noyori's pioneering work in the development of dynamic kinetic resolution (DKR) of β-keto esters via Ru-catalyzed hydrogenation,[4] our group has recently disclosed a protocol for the Ru(II)-catalyzed dynamic kinetic reduction via asymmetric transfer hydrogenation (DKR-ATH) of β-stereogenic-α-keto esters affording secondary glycolic acid derivatives (Scheme 1, eq. a).[5] Our group's longstanding interest in the synthesis of

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complex fully substituted glycolates[6] prompted us to investigate reaction manifolds for the dynamic addition of carbon nucleophiles to β-stereogenic-α-keto esters to provide access to products of this type (eq. b). In order for a DyKAT to be realized, a catalyst must be identified that can effectively racemize the α-keto ester without promoting self-condensation while also activating the nucleophile and delivering it with high stereoselection into a hindered ketone. We postulated that the identity of the β-substituent of the α-keto ester would be important in promoting the desired reactivity due to its direct impact on both the β-C–H acidity and steric environment about the ketone. To this end, β-halo-α-keto esters were selected to investigate this potential reactivity profile due to their previous success in DKR reactions.[5b,7]

We commenced our investigation by exploring the Henry addition of nitromethane to β-bromo-α-keto ester **1** (Table 1). A number of methods have been reported for the Henry addition into pyruvates;[8] however, there is limited precedent for non-pyruvic alkyl α-keto esters and β-branched substrates.[9] Quinidine (**I**) was found to catalyze the nitroaldol addition of (±)-**1a** in quantitative yield with good diastereoselectivity albeit poor enantioselectivity (entry 1). Although bifunctional catalysts **II** and **III** only provided marginal improvements in enantioselectivity employing DCM (entries 2 and 3), a solvent screen revealed that **III** in methyl *tert*-butyl ether (MTBE) provided **2a** in >20:1 dr and 92.5:7.5 er (entry 6). Catalyst modifications to the secondary alcohol led to the identification of *o*-toluoyl-substituted **IV** as the optimized catalyst structure (entry 7). Attempts to further enhance the selectivity through the addition of tetrabutylammonium bromide (TBABr)[7a] or lowering the reaction temperature to 0 °C provided no improvement (entries 8 and 9). Gratifyingly, the ^{i}Pr ester (±)-**1b** provided **2b** in 96:4 er as a single diastereomer when **IV** was employed in 2Me-THF (entry 11). Under these optimized reaction conditions employing the pseudo-enantiomeric catalyst **V**, *ent*-**2b** can be obtained in >20:1 dr and 87:13 er (entry 12).

During the course of our optimization of Henry conditions, we observed that L-proline (**A**) catalyzed the addition of acetone to (±)-**1b**, providing *ent*-**3b** in quantitative yield and 96:4 er albeit in low diastereoselectivity (Table 2, entry 1). Although related to the L-proline-catalyzed DKRs recently reported by Zhang on highly activated 2-oxo-3-aryl-succinates and α,γ-diketo esters,[10] we sought to develop a DyKAT on the less activated β-bromo-α-keto ester (±)-**1b**. A number of direct acetone aldolization reactions with α-keto esters have been reported employing a range of catalysts.[11,12] We chose to examine catalysts derived from the cinchona alkaloids based on their success in the Henry reaction (Table 1). Cinchonidine-derived primary amine catalyst **B** with *p*-nitrobenzoic acid (PNBA) as cocatalyst in acetone:dioxane (1:9) delivered *ent*-**3b** in good diastereo- and enantioselectivity (entry 2). An examination of other polar solvents did not provide satisfactory improvement (entries 3–5); however, reaction with **B** run neat in acetone provided *ent*-**3b** in 95.5:4.5 er as a single diastereomer (entry 6). Attempts to further increase the enantioselectivity employing either **C** or **D** proved ineffective (entries 7 and 8), but pseudo-enantiomeric **E** provided slight improvement delivering **3b** quantitatively with 96:4 er as a single diastereomer (entry 9).

With optimized reaction conditions in hand, we probed the scope of both the direct Henry and acetone aldolization DyKATs of β-bromo-α-keto esters (Table 3). In addition to phenyl (**2b** and **3b**), the reactions were tolerant of both *ortho*- and *para*-substituted aryl groups at the γ-position providing aldol adducts **2b–2d** and **3b–3d** in high yield and selectivity. Heteroaryl (±)-**1e** also reacted efficiently under the reaction conditions cleanly providing **2e** and **3e**. A range of linear alkyl substrates underwent aldolization with no loss in selectivity providing **2g–2i** and **3g–3i** in similarly high efficiency suggesting that aromatic interactions between substrate and catalyst are not required for high levels of selectivity. The increased steric requirements of γ-branching resulted in low diastereoselection and moderate

enantioselection in the formation of **2j** and **3j**. The absolute configuration of (2*R*,3*R*)-**2b** and (2*R*,3*R*)-**3e** was in each case determined by x-ray crystallography and the other products were assigned by analogy.[13]

Given that catalysts **IV** and **E** are derived from cinchona alkaloids, their pseudo-enantiomeric catalysts **V** and **B** are readily available and provide access to both enantiomeric series of Henry and acetone aldolization adducts. Although **V** provides *ent*-**2b** in only 87:13 er, a single recrystallization provides enantioenrichment to 99:1 er. The utility of these reactions is highlighted not only by the mild, operationally simple reaction conditions, but by the near quantitative yield of products obtained following a simple filtration of the crude reaction mixtures through a plug of silica gel obviating the need for aqueous workup.

In order to better understand the mechanistic nuances of the DyKAT, we sought to elucidate the racemization pathway of this reaction. During the development of an “interrupted” Feist–Bénary reaction, Calter proposed that the reaction of 1,3-diketones with β-bromo-α-keto esters proceeds via DKR, where halide S_N2 displacement is promoted by TBABr or TBAI (Scheme 3a).[7] Since our reactions do not generate stoichiometric bromide and addition of TBABr provided no improvement (Scheme 3b), we sought to examine the nature of our dynamic system by studying the Henry reaction as a representative system.

We began our studies by monitoring the enantiomeric compositions of both starting material and product during the course of the reaction of (*R*)-**1b**.[14] While substrate racemization is obligatory to successful dynamic kinetic resolutions and certain DyKAT subtypes, this assay is seldom performed.[2e, 15] This experiment confirmed that the product, (2*R*,3*R*)-**2b**, is obtained in uniform selectivity and that starting material remains racemic throughout the entire course of the reaction. Notably, (*R*)-**1b** is racemized in less than 30 min to (±)-**1b** in the presence of **IV**, highlighting the configurational lability of β-bromo-α-keto esters under general base catalysis (Scheme 4a). Conducting the catalyzed Henry addition with CD_3NO_2 resulted in a primary kinetic isotope effect (k_H/k_D = 2.8) and only 36% D incorporation at the β-position (Scheme 4b).[16] These data suggest that racemization is at least partially an intimate ion process with protonation from the ammonium salt (protonated catalyst) rather than nitromethane, and generation of the reactive nitronate species contributes to the overall reaction rate. *In situ* monitoring of the reaction by No-D ^{1}H NMR spectroscopy[17] in 2-MeTHF revealed no intermediates, confirming that the catalyst resting state is the neutral amine and corroborating that nitronate formation is an uphill process.

Since racemization of **1b** is catalyst-mediated via a chiral onium enolate, the Henry addition is proceeding through a DyKAT.[1c] The moderate deuterium incorporation excludes a DyKAT Type II mechanism wherein the chiral onium enolate would directly participate in an ene-type reaction with *aci*-nitromethane.[18] Calter employed a pyrimidinyl-bridged bis(quinidine) catalyst in their “interrupted” Feist–Bénary reaction to overcome poor selectivities observed with quinidine itself suggesting that both chiral amines may be involved in the enantio-determining step. Non-linear effects have been sparingly studied with cinchona-derived catalysts.[19] To elucidate if a non-linear effect was observed in our Henry reaction, we employed a mixture of pseudo-enantiomeric catalysts **IV** and **V**. The Henry reaction was found to exhibit a linear relationship between catalyst diastereomeric composition and reaction enantioselectivity (R^2 = 0.997), eliminating the possibility of a dimeric catalyst species with concomitant activation of electrophile and nucleophile (Figure 1). Based on these collective data, we propose that the reaction proceeds through a DyKAT Type I manifold (Scheme 5).[20]

In conclusion, dynamic kinetic asymmetric transformations of β-bromo-α-keto esters have been developed employing direct aldolization of nitromethane and acetone. The fully

substituted β-bromo-α-glycolic acid derivatives are obtained with high levels of diastereo- and enantioselectivity in near quantitative yield. The operationally simple protocols offer rapid generation of molecular complexity through formation of vicinal stereocenters in a single C–C bond forming event. Mechanistic studies provide evidence for a DyKAT Type I manifold in the Henry addition of nitromethane into β-bromo-α-keto esters. Extensions of this work and discovery of new dynamic reaction manifolds employing α-labile carbonyls is of ongoing interest in our laboratory.

Experimental Section

Henry aldol

A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **1b** (59.8 mg, 0.20 mmol, 1.0 equiv) and $MeNO_2$ (110 μL, 2.00 mmol, 10.0 equiv) in 2Me-THF (1.0 mL, 0.2 M). Catalyst **IV** (8.6 mg, 0.02 mmol, 0.1 equiv) was added, the vial was capped, and the reaction was allowed to stir for 18 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 × 2 mL) and concentrated *in vacuo* to afford analytically pure **2b** (69.9 mg, 97% yield, >20:1 dr) as a white solid (mp: 113–116 °C).

Acetone aldol

A 1 dram vial equipped with a magnetic stir bar was charged with β-bromo-α-keto ester **1b** (59.8 mg, 0.20 mmol, 1.0 equiv) in acetone (1.0 mL, 0.2 M). Catalyst **E** (5.9 mg, 0.02 mmol, 0.1 equiv) and PNBA (6.7 mg, 0.04 mmol, 0.2 equiv) were added, the vial was capped, and the reaction was allowed to stir for 12 h at room temperature. The reaction was filtered through a 2 cm pad of SiO_2 washing with Et_2O (5 × 2 mL) and concentrated *in vacuo* to afford analytically pure **3b** (67.9 mg, 95% yield, >20:1 dr) as a white solid (mp: 103–105 °C).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

[1]. a) Huerta FF, Minidis ABE, Bäckvall J-E. Chem. Soc. Rev. 2001; 30:321–331.b) Pellissier H. Tetrahedron. 2003; 59:8291–8327.c) Steinreiber J, Faber K, Griengl H. Chem. Eur. J. 2008; 14:8060–8072. [PubMed: 18512868] d) Pellissier H. Tetrahedron. 2008; 64:1563–1601.e) Pellissier H. Adv. Synth. Catal. 2011; 353:659–676.f) Pellissier H. Tetrahedron. 2011; 67:3769–3802.

[2]. a) Reyes E, Córdova A. Tetrahedron Lett. 2005; 46:6605–6609.b) Córdova A, Ibrahem I, Casas J, Sundén H, Engqvist M, Reyes E. Chem. Eur. J. 2005; 11:4772–4784. [PubMed: 15929141] c) Parsons AT, Johnson JS. J. Am. Chem. Soc. 2009; 131:3122–3123. [PubMed: 19256562] d) Zhao G-L, Ullah F, Deiana L, Lin S, Zhang Q, Sun J, Ibrahem I, Dziedzic P, Córdova A. Chem. Eur. J. 2010; 16:1585–1591. [PubMed: 20039352] e) Campbell MJ, Johnson JS, Parsons AT, Pohlhaus PD, Sanders SD. J. Org. Chem. 2010; 75:6317–6325. [PubMed: 20863142] f) Parsons AT, Smith AG, Neel AJ, Johnson JS. J. Am. Chem. Soc. 2010; 132:9688–9692. [PubMed: 20572661]

[3]. For a recent example of enantioconvergent aldolization of α-stereogenic aldehydes: Bergeron-Brlek M, Teoh T, Britton R. Org. Lett. 2013; 15:3554–3557. [PubMed: 23819733]

[4]. a) Noyori R, Ikeda T, Ohkuma T, Widhalm M, Kitamura M, Takaya H, Akutagawa S, Sayo N, Saito T. J. Am. Chem. Soc. 1989; 111:9134–9135.b) Kitamura M, Tokunaga M, Noyori R. J. Am. Chem. Soc. 1993; 115:144–152.c) Noyori R, Tokunaga M, Kitamura M. Bull. Chem. Soc. Jpn. 1995; 68:36–55.

[5]. a) Steward KM, Gentry EC, Johnson JS. J. Am. Chem. Soc. 2012; 134:7329–7332. [PubMed: 22509806] b) Steward KM, Corbett MT, Goodman CG, Johnson JS. J. Am. Chem. Soc. 2012; 134:20197–20206. [PubMed: 23186551] c) Corbett MT, Johnson JS. J. Am. Chem. Soc. 2013; 135:594–597. [PubMed: 23297694] d) Goodman CG, Do DT, Johnson JS. Org. Lett. 2013; 15:2446–2449. [PubMed: 23631467]

[6]. a) Nicewicz DA, Johnson JS. J. Am. Chem. Soc. 2005; 127:6170–6171. [PubMed: 15853312] b) Boyce GR, Greszler SN, Johnson JS, Linghu X, Malinowski JT, Nicewicz DA, Satterfield AD, Schmitt DC, Steward KM. J. Org. Chem. 2012; 77:4503–4515. [PubMed: 22414181] c) Boyce GR, Liu S, Johnson JS. Org. Lett. 2012; 14:652–655. [PubMed: 22235777] d) Schmitt DC, Malow EJ, Johnson JS. J. Org. Chem. 2012; 77:3246–3251. [PubMed: 22394389] e) Corbett MT, Uraguchi D, Ooi T, Johnson JS. Angew. Chem. 2012; 124:4763–4767.Angew. Chem. Int. Ed. 2012; 51:4685–4689.f) Slade MC, Johnson JS. Beilstein J. Org. Chem. 2013; 9:166–172. [PubMed: 23399952]

[7]. a) Calter MA, Phillips RM, Flaschenriem C. J. Am. Chem. Soc. 2005; 127:14566–14567. [PubMed: 16231897] b) Calter MA, Li N. Org. Lett. 2011; 13:3686–3689. [PubMed: 21667928]

[8]. a) Christensen C, Juhl K, Jørgensen KA. Chem. Commun. 2001:2222–2223.b) Christensen C, Juhl K, Hazell RG, Jørgensen KA. J. Org. Chem. 2002; 67:4875–4881. [PubMed: 12098300] c) Lu S-F, Du D-M, Zhang S-W, Xu J. Tetrahedron: Asymmetry. 2004; 15:3433–3441.d) Du D-M, Lu S-F, Xu J. J. Org. Chem. 2005; 70:3712–3715. [PubMed: 15845012] e) Choudary BM, Ranganath KVS, Pal U, Kantam ML, Sreedhar B. J. Am. Chem. Soc. 2005; 127:13167–13171. [PubMed: 16173743] f) Blay G, Hernández-Olmosa V, Pedro JR. Org. Biomol. Chem. 2008; 6:468–476. [PubMed: 18219416] g) Bulut A, Aslan A, Dogan Ö. J. Org. Chem. 2008; 73:7373–7375. [PubMed: 18700743] h) Uraguchi D, Ito T, Nakamura S, Sakaki S, Ooi T. Chem. Lett. 2009; 38:1052–1053.i) Xu H, Wolf C. Synlett. 2010:2765–2770.j) Miyake GM, Iida H, Hu H-Y, Tang Z, Chen EY-X, Yashima E. J. Polym. Sci. A: Polym. Chem. 2011; 49:5192–5198.

[9]. a) Li H, Wang B, Deng L. J. Am. Chem. Soc. 2006; 128:732–733. [PubMed: 16417358] b) Qin B, Xiao, Liu X, Huang J, Wen Y, Feng X. J. Org. Chem. 2007; 72:9323–9328. [PubMed: 17973533]

[10]. a) Wang Y, Shen Z, Li B, Zhang Y, Zhang Y. Chem. Commun. 2007:1284–1286.b) Yang J, Wang T, Ding Z, Shen Z, Zhang Y. Org. Biomol. Chem. 2009; 7:2208–2213. [PubMed: 19421462]

[11]. For seminal catalytic, enantioselective Mukaiyama aldol additions to α-keto esters: Evans DA, Kozlowski MC, Burgey CS, MacMillan DWC. J. Am. Chem. Soc. 1997; 119:7893–7894. Evans DA, MacMillan DWC, Campos KR. J. Am. Chem. Soc. 1997; 119:10859–10860. Evans DA, Burgey CS, Kozlowski MC, Tregay SW. J. Am. Chem. Soc. 1999; 121:686–699.

[12]. a) Tang Z, Cun L-F, Cui X, Mi A-Q, Jiang Y-Z, Gong L-Z. Org. Lett. 2006; 8:1263–1266. [PubMed: 16562867] b) Xu X-Y, Tang Z, Wang Y-Z, Luo S-W, Cun L-F, Gong L-Z. J. Org. Chem. 2007; 72:9905–9913. [PubMed: 18004868] c) Liu Q-Z, Wang X-L, Luo S-W, Zheng B-L, Qin D-B. Tetrahedron Lett. 2008; 49:7434–7437.d) Jiang Z, Lu Y. Tetrahedron Lett. 2010; 51:1884–1886.e) Li P, Zhao J, Li F, Chan ASC, Kwong FY. Org. Lett. 2010; 12:5616–5619. [PubMed: 21070050] f) Kan S-S, Li J-Z, Ni C-Y, Liu Q-Z, Kang T-R. Molecules. 2011; 16:3778–3786. [PubMed: 21544040] g) Peng L, Wang L-L, Bai J-F, Jia L-N, Guo Y-L, Luo X-Y, Wang F-Y, Xu X-Y, Wang L-X. Org. Biomol. Chem. 2011; 9:4774–4777. [PubMed: 21614388] h) Zhu X, Lin A, Fang L, Li W, Zhu C, Cheng Y. Chem. Eur. J. 2011; 17:8281–8284. [PubMed: 21656582] i) Viózquez SF, Bañón-Caballero A, Guillena G, Nájera C, Gómez-Bengoa E. Org. Biomol. Chem. 2012; 10:4029–4035. [PubMed: 22514086]

[13]. CCDC 951438 ((2*R*,3*R*)-**2b**) and 951439 ((2*R*,3*R*)-**3e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14]. See the supporting information for experimental details and data.

[15]. Wegman MA, Hacking MAPJ, Rops J, Pereira P, van Rantwijk F, Sheldon RA. Tetrahedron: Asymmetry. 1999; 10:1739–1750.

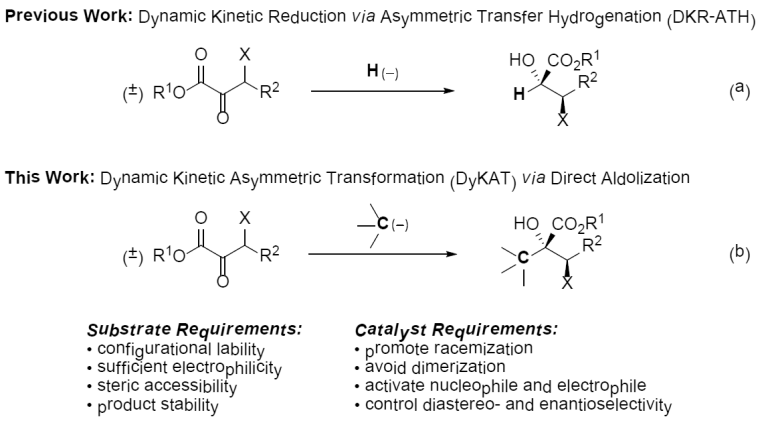
[16]. The kinetic isotope effect was measured by comparison of initial rates from parallel experiments with CH_3NO_2 and CD_3NO_2. See the supporting information for further experimental details.

[17]. Hoye TR, Eklov BM, Ryba TD, Voloshin M, Yao LJ. Org. Lett. 2004; 6:953–956. [PubMed: 15012073]

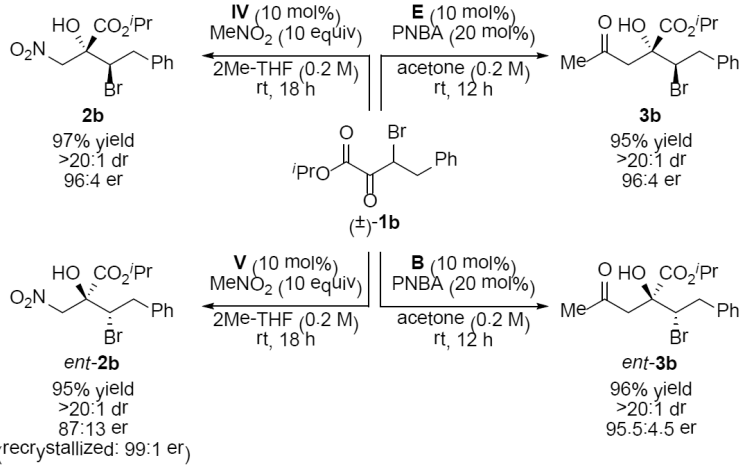
[18]. The possibility of this mechanism was suggested to us by Professor T. Rovis (Colorado State University).

[19]. a) Huck W-R, Mallat T, Baiker A. Catal. Lett. 2003; 87:241–247.b) Huck W-R, Bürgi T, Mallat T, Baiker A. J. Catal. 2003; 216:276–287.c) Ma Z, Zaera F. J. Am. Chem. Soc. 2006; 128:16414–16415. [PubMed: 17177346] d) Ogura Y, Akakura M, Sakakura A, Ishihara K. Angew. Chem. 2013; 125:8457–8461.Angew. Chem. Int. Ed. 2013; 52:8299–8303.

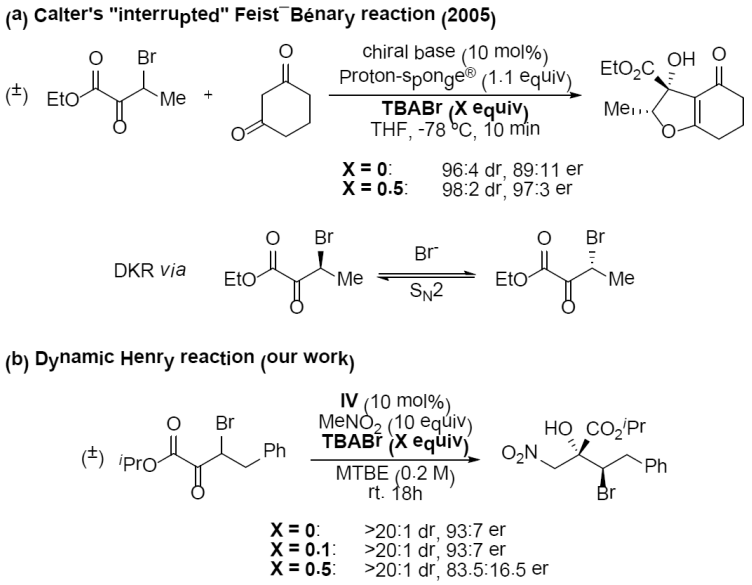
[20]. A reviewer pointed out that it might be simpler to classify these reactions as dynamic kinetic resolutions. Admittedly, the differences in the present case are subtle. According to the Steinreiber definition (reference 1c), DyKAT reactions take place via interconverting diastereomeric complexes where rate differences might reasonably be expected (or possible) for conversion of the enantiomeric starting materials to the “locally achiral” intermediate. This requirement is often taken to mean that the chiral catalyst that mediates the productive asymmetric transformation also catalyzes substrate racemization, a scenario that is certainly operative in the present case. We presume that diastereomeric precomplexes form between the substrate and the bifunctional catalyst prior to proton transfer, in analogy to soft enolization.



Scheme 1.
Development of a DyKAT of β-stereogenic-α-keto esters.

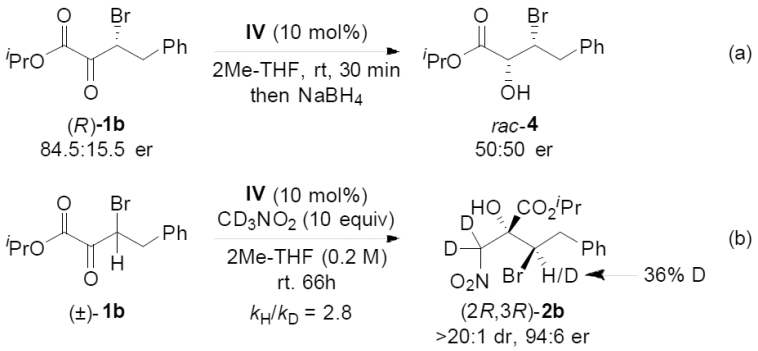


Scheme 2.
Access to both enantiomeric series.

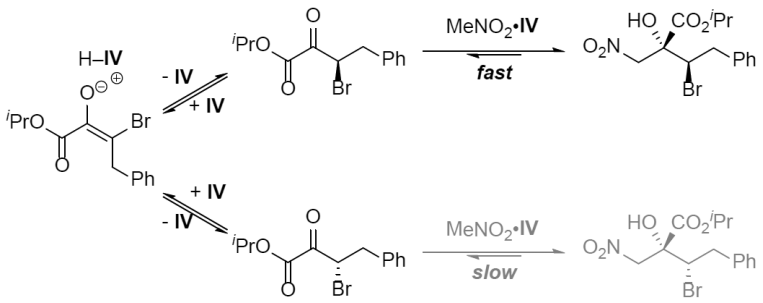


Scheme 3.

Dynamic kinetic resolution *via* halide S_N2 displacement.



Scheme 4.
Racemization and deuterium labeling studies.



Scheme 5.
Proposed DyKAT mechanism.

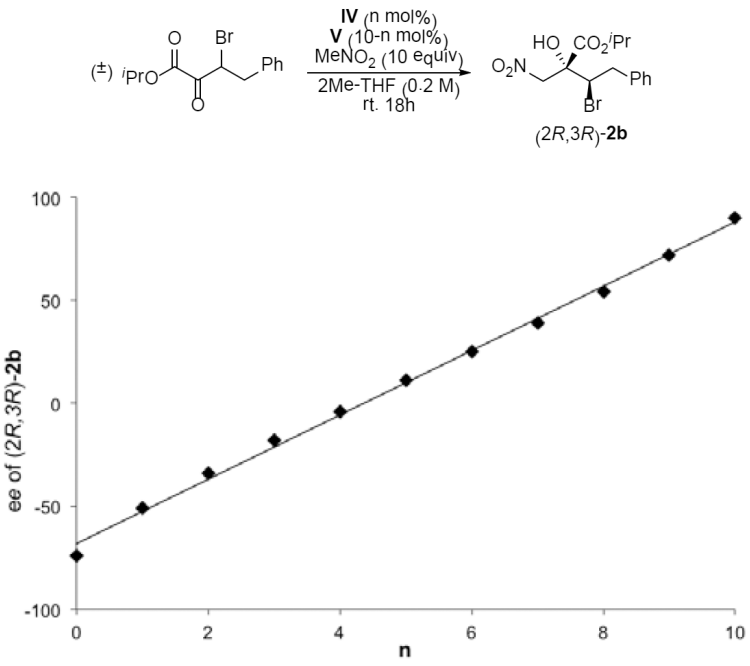
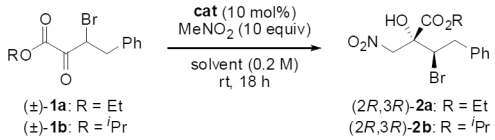
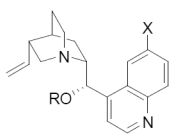


Figure 1.
Evaluation of nonlinear effects in catalyzed Henry reactions.

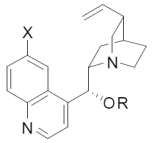
Table 1

Henry DyKAT Optimization[a]





I: X = OMe, R = H
II: X = OH, R = H
III: X = OH, R = Benzoyl
IV: X = OH, R = *o*-Toluoyl



V: X = OH, R = *o*-Toluoyl

entry	1	cat	solvent	dr[b]	er[c]
1	**1a**	**I**	DCM	13:1	62:38
2	**1a**	**II**	DCM	12:1	72:28
3	**1a**	**III**	DCM	11:1	80:20
4	**1a**	**III**	toluene	16:1	80.5:19.5
5	**1a**	**III**	MeCN	>20:1	88:12
6	**1a**	**III**	MTBE	>20:1	92.5:7.5
7	**1a**	**IV**	MTBE	>20:1	93:7
8[d]	**1a**	**IV**	MTBE	>20:1	93:7
9[e]	**1a**	**IV**	MTBE	>20:1	93:7
10	**1b**	**IV**	MTBE	>20:1	92:8
11	**1b**	**IV**	2Me-THF	>20:1	96:4
12	**1b**	**V**	2Me-THF	>20:1	13:87

[a] Reactions were performed on 0.20 mmol scale and proceeded to full conversion as adjudged by TLC.

[b] Determined by ^{1}H NMR analysis of crude material.

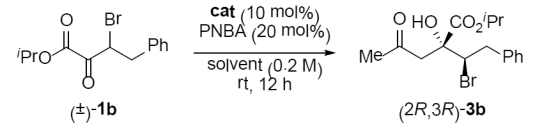
[c] Determined by chiral HPLC analysis.

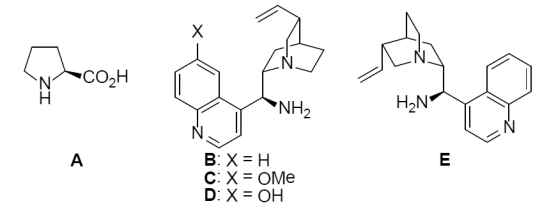
[d] With TBABr (10 mol%) as an additive.

[e] Reaction performed at 0 °C for 30 h.

Table 2

Acetone Aldol DyKAT Optimization[a]





entry	cat	solvent	dr[b]	er[c]
1[d]	**A**	acetone	2:1	4:96
2	**B**	acetone:dioxane (1:9)	14:1	12:88
3	**B**	acetone:EtOAc (1:9)	8:1	19.5:80.5
4	**B**	acetone:MeCN (1:9)	5:1	16:84
5	**B**	acetone:DMF(1:9)	9:1	9.5:90.5
6	**B**	acetone	>20:1	4.5:95.5
7	**C**	acetone	>20:1	10.5:89.5
8	**D**	acetone	>20:1	14.5:85.5
9	**E**	acetone	>20:1	96:4

[a] Reactions were performed on 0.20 mmol scale and proceeded to full conversion as adjudged by TLC.

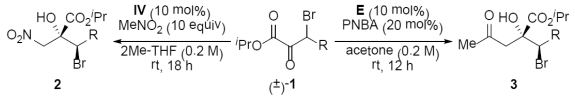
[b] Determined by ^{1}H NMR analysis of crude material.

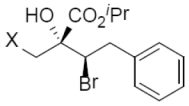
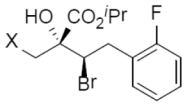
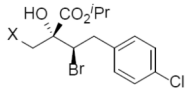
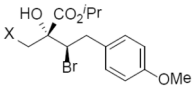
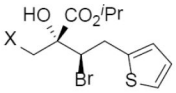
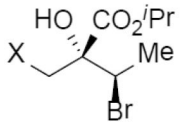
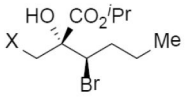
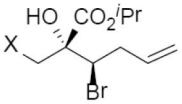
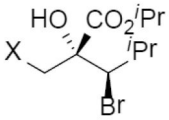
[c] Determined by chiral HPLC analysis.

[d] Reaction performed with **A** (20 mol%) in the absence of PNBA for 3 h.

Table 3

Substrate Scope for DyKATs[a]



2b: X = NO_2 97% yield >20:1 dr 96:4 er		**3b**: X = Ac 95% yield >20:1 dr 96:4 er
2c: X = NO_2 97% yield >20:1 dr 92:8 er		**3c**: X = Ac 95% yield >20:1 dr 95.5:4.5 er
2d: X = NO_2 98% yield >20:1 dr 95.5:4.5 er		**3d**: X = Ac 97% yield >20:1 dr 96.5:3.5 er
2e: X = NO_2 98% yield >20:1 dr 96:4 er		**3e**: X = Ac 93% yield >20:1 dr 96:4 er
2f: X = NO_2 92% yield >20:1 dr 94.5:5.5 er		**3f**: X = Ac 96% yield >20:1 dr 95.5:4.5 er
2g: X = NO_2 95% yield >20:1 dr 94:6 er		**3g**: X = Ac 96% yield >20:1 dr 95.5:4.5 er
2h: X = NO_2 96% yield 17:1 dr 93:7 er		**3h**: X = Ac 94% yield >20:1 dr 95.5:4.5 er
2i: X = NO_2 98% yield >20:1 dr 94.5:5.5 er		**3i**: X = Ac 95% yield >20:1 dr 96:4 er
2j:[b] X = NO_2 95% yield 5:1 dr 87:13 er		**3j**: X = Ac 90% yield 2.5:1 dr 90:10 er

[a] Reactions were performed on 0.20 mmol scale. Yield of isolated product reported. Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of crude material. Enantiomeric ratio (er) determined by chiral HPLC analysis.

[b] Reaction performed for 42 h.